TUMORS OF THE EYE AND ORBIT*

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UNCONTROLLED growths of cells without biologic purpose involving the eye are, in the main, not unlike those found elsewhere in the body. In the beginning they have a special local importance and the undifferentiated types have a general significance as well. The relative frequency of benign and malignant tumors in the eye may be explained by the presence of many mixed, interrelated tissues, each dependent on the other, which compose this highly specialized organ. Since the eye lends itself well to examination, tumors are usually observed in their very early stages. But because anatomical or inflammatory changes frequently resemble growths they are not always distinguished and treated promptly and properly.

The tumors which may arise in the eye and its adnexa, and in the orbit are innumerable and discussion of them is quite beyond the time allotted for this presentation. I shall devote the period to recent contributions to the subject and to controversial issues. My material will be presented simultaneously with the showing of illustrations of a number of tumors which were drawn from cases seen at the Eye Institute and with slides indicating the value of the x-ray in the study of expanding lesions of the orbit.

Congenital *naevi* of the bulbar conjunctiva are open to discussion on two points: first, their frequency as the origin of malignant growth and secondly, their relation to benign melanomas of the interior of the eye. The naevus is of neural origin, derived from the end apparatus of the sensory nerve, is usually pigmented and may not be apparent at birth. It is essentially a benign neoplasm which grows very slowly, passes through a long period of quiescence and may eventually atrophy. According to most authors a sudden stimulus to rapid growth may occur, in which event the tumor acquires a capacity to become highly

* Presented October 17, 1946 in the Nineteenth Graduate Fortnight of The New York Academy of Medicine. From the Institute of Ophthalmology of the Presbyterian Hospital.

malignant. The distinguishing cell of the mole is the large naevus cell which is round or polygonal in shape. These cells may present a gland-like appearance and are found beneath down-dipping prolongations of the surface epithelium. The melanin found in the growth is mainly intracellular, more abundant near the surface and in the central-lying epithelium. Cysts are very frequently present.

The nature and ontogeny of the naevus cells have given rise to much controversy. Masson's[1] recent exposition of the subject that these cells are neither epithelial nor mesoblastic in character but neuro-ectodermal and associated with the terminal neural apparatus is now generally accepted. They are seen associated with the medulated and non-medulated nerve fibres, ending in the skin in Meissner's corpuscles. Some of these cells, less closely associated with the nerves produce pigment (melanoblasts). Wherever a discussion of the naevus is found, one encounters reports of malignant melanoma arising in the naevus. Reese[2] wrote in 1943 that he had never encountered this circumstance in the eye and in a study of those cases reported in the literature, only two cases could be found which could be identified definitely as cases of melanoma which arose from a pre-existing naevus. He believes that precancerous melanosis may have been mistaken for the mole or that the melanoma was acquired and malignant from the beginning.

The melanomata seen in the iris or choroid are also regarded as naevi but since true naevus cells are not found in these lesions, doubt exists that they are the same. The spindle cells without the processes characteristic of choroidal chromatophores have been regarded as atypical naevus cells. The many references to malignancy arising in naevi in the literature apply to the pigmented spots of the iris or choroid. Reese[3] has called attention to the frequency of pigmented spots or freckles in the iris in cases of malignant melanoma. Many others have written of the coexistence of benign melanomata of the choroid with a uveal sarcoma. This has occurred sufficiently often to justify the periodical examination of eyes with benign melanomata. Duke-Elder[4] has stressed that the occurrence of glaucoma in an eye with a naevus should always be looked upon with the greatest suspicion. By naevus here he is again speaking of a melanoma. Incomplete excision of a melanoma may lead to rapid and uncontrollable growth, as was the circumstance in the case reported by Greenwood.[5]

Reese[2] has described acquired *precancerous melanosis* as a diffuse,

non-elevated pigmentation with a granular and ofttimes dull appearance of the conjunctiva, appearing usually during the fifth decade of life and showing malignant change in 5 to 10 years. Occasionally the melanosis is malignant from the beginning. It may become so diffuse as to involve almost all the bulbar and palpebral conjunctiva and adjacent skin without causing any localized tumor mass.

Acquired precancerous melanosis has distinguishing histologic characteristics in the benign and in the malignant phase, is radio-sensitive in the precancerous stage and radio-resistant in the malignant. Patients observed by Reese in the malignant stage died. Early exenteration is the treatment advised. Precancerous melanosis should not be confused with 1) congenital melanosis of conjunctiva, 2) melanosis oculi and 3) naevi.

From the several papers which have appeared in the literature in recent years on the prognosis in *malignant melanoma* of the uvea, one gains the impression that this tumor is not as malignant as it was formerly thought to be. Certainly it is not to be compared in malignancy with those arising elsewhere in the body. In their study of 500 malignant melanomas of the eye followed over a period of five years or longer, Callender, Wilder and Ash[6] of the Army Medical Museum found a mortality of 48 per cent. In 200 cases followed ten years or more, the percentage of deaths rose to sixty-six. They found the average duration of life following operation to be forty-six months. These authors have made a significant contribution to pathology in their study of the malignancy of the various types of malignant melanomas according to cellular structure, reticulin and pigment content.

The single spindle cell variety shows a relatively low degree of malignancy and a heavy fibre content is also evidence of a low degree of malignancy. An increased degree of malignancy is associated with the epithelioid type of malignant melanoma. It was suggested that an increase of malignancy is associated with increased pigment content. Thus, on the basis of microscopic appearance, an opinion can be expressed by the pathologist on the degree of malignancy indicated by the composition of the tumor.

A notable contribution to the treatment of *retinoblastoma* by radiation has been made by Martin and Reese.[7] In 11 of 24 cases of bilateral retinoblastoma managed by them vision was preserved to some degree by their technique. These authors enucleated the eye with the

more advanced tumor and treated the remaining eye by fractionated doses of roentgen ray totalling 8000 r to each of two portals; 2½ cm. cones were employed and aligned in such a manner as to exclude the anterior segment of the eye from the field. After the tumor atrophied under the treatment the contained calcium became increasingly apparent and finally could be seen as a small bag of concretions. The surrounding retina formerly occupied by the tumor appeared as an atrophic area with proliferation of pigment. This treatment is applicable in those cases in which the tumor is localized to relatively small areas of the retina.

That the calcium content of retinoblastoma may be utilized in the differential diagnosis of the tumor was advanced by Pfeiffer[8] who found calcium granules in 80 per cent of all of the tumors studied histologically and roentgenographically. Shadows of calcium have never been demonstrated in conditions resembling retinoblastoma.

Aside from epitheliomas of the eyelids which are superficial and easily recognized, *tumors of the orbit* usually displace the eye, or in other words, produce exophthalmos. The diagnosis of tumor of the orbit then involves a study of exophthalmos which may be due to a number of conditions other than hyperthyroidism and tumor. Exophthalmos produced by tumor is usually unilateral but here again the unilateral displacement of the eye is as frequently produced by other conditions. In a series of 200 consecutive cases of exophthalmos studied by roentgenography[9] the displacement of the eye was caused by benign and malignant tumors and cysts in seventy-two or 36 per cent of all cases. In only 10 per cent of all the cases was exophthalmos produced by a malignant tumor. There were thirteen primary intraorbital neoplasms, eight sarcomas and five mixed tumors of the lacrymal gland in the series. The orbit was involved secondarily in eight cases in which five derived from malignant neoplasm arising in the nasal fossa or sinuses, two from basal cell epitheliomas and one from a myeloma. In the diagnosis of orbital tumor, therefore, a vast number of other conditions have to be excluded. This can best be done by roentgenographic study. In this series of 200 cases there were positive roentgenographic findings in nearly 70 per cent and in 42 per cent of all the cases the findings were diagnostic. Six conditions, that is, retention cyst of a paranasal sinus, meningioma, craniostenosis, neurofibromatosis, deformity of the orbit, and glioma of the optic nerve made up one-third of all

the cases and invariably produced changes which are indicative in the x-ray film.

One of the most confusing conditions in the diagnosis of lesions of the orbit which, in addition, is one of the most common single causes of exophthalmos, is chronic granuloma or so-called *pseudo-tumor* of the orbit. The cause of this inflammatory involvement, which is more frequently unilateral than bilateral and which tends to run a self-limited course, is not known. Lymphoblastoma has been associated in a number of cases. Fortunately, chronic granuloma can be differentiated in most cases by the history and clinical findings and absence of x-ray changes. The onset of this condition is rather sudden, the eyelids are edematous, the exophthalmos is frequently severe, a palpebral mass may be encountered and, in many cases, there is interference with ocular motility. Reese[10] analyzed 30 cases of the literature and found that in 50 per cent of them the patient had been subjected to exenteration of the orbit for supposed malignant neoplasm. Lewis[11] stressed the difficulty of getting correct diagnoses from many general pathologists who, he found, are more likely to report that the biopsy tissue represents a true neoplasm.

The paper by McGavic[12] on "*lymphomatoid diseases involving the eye*" deserves notice for its calls attention to a complex tumor of unknown pathogenesis with different criteria for histopathologic and hematologic diagnosis of the recognized entities. Failure to recognize lymphomatoid diseases as everchanging processes requiring repeated biopsies of tissue and repeated studies of the blood through the clinical course has delayed the adoption of a uniform classification of the many types of abnormal lymphoid reactions. McGavic's paper dealt with 21 verified cases in an effort to contribute toward a working basis for the management of patients with lymphomatoid diseases of the eye. He classified his cases as to histologic type. The three most important types given were simple lymphoma or lymphocytic celled lymphosarcoma, giant follicular lymphosarcoma and reticulin cell lymphosarcoma. Repeated differential blood counts in studies of the bone marrow were necessary to rule out or demonstrate leukemic changes.

The general outlook for patients with lymphomatoid disease is poor. With treatment approximately 15 per cent survived a five year period of observation. Lymphomatoid growths are radiosensitive but this quality must be differentiated from radiocurability. A given lesion

may be treated to complete regression but this does not preclude the appearance of tumor masses in other sites. The use of radiation in the region of the eye is, of course, a threat to the eye.

McGavic reported one case diagnosed as pseudo-tumor (granuloma of the orbit) on biopsy specimen which subsequently developed generalized lymphadenopathy. On biopsy of a supra-clavicular lymph node the diagnosis of a reticulin celled lymphosarcoma was made. In reviewing the case, McGavic stated that the disease was a changing lymphomatoid process but first appeared to be inflammatory.

I have a patient under observation at the present time with exophthalmos which was diagnosed pseudo-tumor on biopsy specimen, but who has diffuse lymphadenopathy of the adjacent preauricular and cervical nodes and enlargement of the maxillary glands which, I suspect, will be proved to be lymphosarcoma. So far, this patient has shown some local response to radiation of the orbit.

Davis'[13] paper on "*Tumors of the Optic Nerve Associated with Recklinghausen's Disease*" is notable for its splendid review of the subject of tumors of the optic nerve. Gliomas and meningiomas are virtually the only primary tumors of the optic nerve. "The glial tumors start with an abnormal proliferation of the adult types of neuroglia of the nerve stem. After varying periods of growth the abnormal neoplastic neuroglia cells penetrate the pia with the formation of a gliomatous tumor in the sheath. Proliferation of the mesothelial cells of the arachnoid follows the glial penetration of the pia with the formation of a tumorlike mass in this portion of the nerve sheath. Later, intermingling of the proliferated cells from these two areas produces a complex histologic structure. the precise nature of which it is difficult to interpret unless earlier stages of the growth have been studied because histogenesis of the neoplastic cells has not been determined." Such types as spongioblastoma, spongioneuroblastoma, astrocytoma and oligodendryocytoma have been reported. According to Davis the outstanding feature of the neoplastic cells was excessive fibre formation within as well as without the nerve stem. The predominant cell types were astrocytes so that he designated the five tumors of his series associated with Recklinghausen's disease "astrocytomas."

Further, on the basis of his experience, Davis stated that tumors of the optic nerve probably belong to a systemic disease as originally suggested by Emanuel which is borne out by the simultaneous appear-

ance of multiple lesions in the central and the proliferated nervous system, by the fact that the tumors are bilateral at times, and further by the fact that multiple involvement of the nerve has been reported. The slow rate of growth and the relatively benign nature of the tumors are characteristic of other lesions associated with this syndrome.

Cushing's[14, 15, 16] papers on meningiomas give a concise understanding of the origin and behavior of this less common tumor of the optic nerve. Most meningiomas arise within the cranium but since cell clusters of the archnoid are found in the sheath of optic nerve, they may be primary in the orbit. The case of Friedenwald[17] was demonstrated to have arisen within the orbit. One patient in my series with a very large meningioma of the orbital portion of the optic nerve showed a normal optic canal and, at this time, fifteen years since the operation, continues to be well and to have normal vision of the other eye.

Because of the variety of usually unsuitable names which have been applied to various tumors, great confusion exists in the literature in regard to most. Ophthalmologists have persisted in the use of the term "cholesteatoma" for that type of congenital growth which presents a glistening white, nodular appearance and known as "tumeur perlee" by the French. Since this congenital tumor, arising occasionally in the orbit and more frequently within the cranial cavity, appears to have a different origin from those cholesteatomata found associated with middle ear disease, it seems pertinent that a distinction be made.

The indispensable criterion for the diagnosis of these lesions is the microscopic demonstration of epidermoid elements making up the walls of the tumor. We are logically forced to name the growth from its indispensable character and should use the term suggested by Critchley and Ferguson,[18] that is, *epidermoid*. The usual gross appearance of these tumors is that of an irregularly lobulated, white, opaque, glistening ovoid or spherical mass, varying from 1 or less to 10 centimeters in diameter. The tumor is firm but friable and breaks easily on moderate pressure. On section it often gives the appearance of an onion, owing to its laminations. It may leave a fatty stain on the knife and a fatty rancid or fatty odor may be detected. The very old tumors become necrotic, especially in the center and cholesterin crystals are found in this necrotic debris. It is avascular and easily removable.

In the opinion of Horrax[19] the difference between epidermoid and dermoid tumors depends upon the depth of the cell layer from which

the embryonal rest arises. If the cells are derived from the epidermis the resulting tumor is an epidermoid. If, on the other hand, the original cells arose from the dermal layer the tumor contains hair, sebaceous glands and other dermal elements and should be termed "dermoid." This opinion is opposed to that of Boestrom who felt that not the depth of the cell layer but the embryonic age of the cell rest was the determinant. The more primitive and undifferentiated the cells of origin of the tumor, the more likely they are to give rise to dermoid rather than epidermoid tumors. The latter must, therefore, arise fom inclusions occurring later in embryonic life. Clinically the dermoids frequently bring about symptoms at an earlier age in the life of the patient than the epidermoids.

The cholesteatomas associated with infection of the middle ear cavity consist mainly of epithelial debris with fat, granulation tissue, leukocytes and cholesterin crystals and may simply be the accumulated heaping up of excessive desquamation and reaction to inflammation. Erdheim,[20] however, reported a typical epidermoid in the middle ear unassociated with infection. It may be that under the stimulus of the inflammatory process the back growth of the meatal epithelium through the tympanic cavity gives rise to dermoid formation. It is possible, on the other hand, that the tumor may be present in the middle ear as an epithelial rest and its presence predisposes the ear to suppuration so that the infection and tumor formation are discovered in association with each other.

Adrenal sympathicoblastoma or neuroblastoma[21] is one of the commonest causes of exophthalmos in children and might well be mentioned here. This malignant tumor, which is invariably fatal, arises from an embryonal nerve cell derived from neural ectoderm and is the primary sympathetic cell. This tumor has the same embryonic origin as the medulla of the suprarenal gland and the adjacent sympathetic ganglions and may arise from either. The neoplasm arises more frequently from adrenal medulla but it may arise from embryonal sympathetic cells or sympathicoblasts anywhere in the body.

The tumor consists of small cells which have hyperchromatic nuclei, are polymorphous, contain little cytoplasm and lie in dense, new-formed connective tissue. The cells with delicate fibrils are usually densely packed or grouped to present the appearance of an embryonic ganglion of the sympathetic nervous system (Wahl). The cells may also form

a rosette, arranged around a central mass of fibrils. Among these cells, larger round cells may be found, with larger, pale, vesicular nuclei and a larger rim of cytoplasm. These were called embryonic ganglion cells by Lewis and Geschickter. Rosettes are found in approximately 50 per cent of cases and these and/or fibrils should be present for a positive diagnosis according to Leinfelder. Verhoeff wrote that these rosettes are quite different from the rosettes of retinoblastoma.

The ocular signs are preëminent in the diagnosis of the tumor. The occurrence of ecchymosis of one or both lids alone or associated with exophthalmos not only should suggest adrenal sympathicoblastoma but may be diagnostic of the disease. Sturtevant and Kelly emphasized the fact that ecchymosis of the eyelids and proptosis in infants and children should arouse suspicion of adrenal neoplasm. Seefelder stated that these two ocular signs are diagnostic of the source of the orbital metastases. In addition, papilloedema and temporal tumor are frequently found. The metastases to the orbit are probably hematogenous. In the "Pepper type" the outstanding symptoms are local and involve only the lower and periaortic lymph nodes giving rise to abdominal signs, especially to a large liver and metastases to various parts of the skeleton. The average age of cases of the Pepper type is two years and of the Hutchison or cranial type is four to five years.

Because of the limited time and the vastness of the subject assigned to me I could scarcely do more than mention several tumors which seem of special interest at this stage in the development of our knowledge. The reason for choosing these particular neoplasms is apparent in each discussion. But by these reasons, many other tumors could have been included. Malignant melanoma and retinoblastoma required discussion not because they are the commonest tumors of the eye but because recent advances have been made in our understanding and management of them. The series of cases of exophthalmos mentioned seems a fair sample of the great variety of conditions which may cause displacement of the eye. With the x-ray we are able not only to diagnose many causes of exophthalmos but also to differentiate, with some degree of accuracy, at least a few of the various tumors which occur in the orbit.

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